Crystallographic Evidence for Cyclopropane Ring Formation in Isotwistenes Obtained by Thermal Cascade Reactions of Cyclopentadienone with Acyclic Conjugated Dienes

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Received March 2, 2009; accepted April 16, 2009; published online April 16, 2009

The molecular structure of the double Diels–Alder (DDA) adduct derived from three-step thermal cascade reactions of 2,5-bis(methoxycarbonyl)-3,4-diphenylcyclopentadienone with ethyl sorbate is elucidated by single crystal X-ray analysis. The structural features and the reaction mechanism of the adduct are discussed on the basis of density functional theory (DFT) calculation results.

Key words cyclopentadienone; cyclopropane ring; double Diels–Alder reaction; pericyclic reaction; density functional theory calculation; X-ray analysis

Cascade reactions are attractive strategies to construct complex structures in a single step. In previous studies, we reported that the reaction of cyclopentadienones (**1**) with non-conjugated or conjugated dienes (**2**) afforded the double Diels–Alder (DDA) adduct (**5**) *via* three-step thermal cascade pericyclic reactions [addends→DA adduct (**3**)→decarbonylated DA adduct (**4**)→intramolecular DA (IMDA) adduct (**5**)].[1—6]

During the course of this study, we isolated the DDA adducts with a cyclopropane ring produced by the one-pot reactions of 2,5-bis(methoxycarbonyl)-3,4-diphenylcyclopentadienone (**1a**) with ethyl sorbate (**2a**) and 2,4-hexadiene (**2b**); the structures of the DDA adducts were determined from NMR spectral data.[6] Contrary to our expectation, the heat of reaction ($\Delta H_f^{\mathrm{DDA}} - \Delta H_f^{\mathrm{triene}}$) for the IMDA reaction calculated by the semi-empirical molecular orbital (MO) method[7—10] was inconsistent with the experimental result, which showed a positive value for the heat of reaction.[11] This positive value indicates that the IMDA adduct (**5**) is thermodynamically unstable. This result prompted us to further elucidate the structure of **5** by crystallographic analysis and reinvestigate the reaction behavior using high-level MO calculations such as density functional theory (DFT).[12]

Results and Discussion

The heating of **3a**, which was obtained by the cycloaddition of **1a** to ethyl sorbate (**2a**), at 170 °C in the absence of solvent lead to its decarbonylation followed by IMDA reaction to afford the DDA adduct **5a** in 64% yield.[6] Similarly, heating of the DA adduct (**3b**) of 2,4-hexadiene (**2b**) at 210 °C afforded the corresponding DDA adduct (**5b**) in 77% yield.[6] In order to confirm the structure of **5a**, we carried out its single crystal X-ray analysis. The computer-generated structure drawing[13] of **5a**, with atoms represented by numbering system, is shown in Fig. 1.

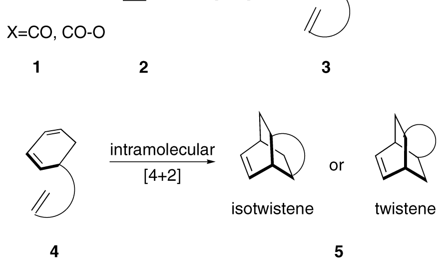

Chart 1

As observed in this figure, the structure of **5a** confirmed that it is a DDA adduct containing a cyclopropane ring (C6–C1–C7, 61.9°; C1–C6–C7, 58.1°; C6–C7–C1, 60.0°). The DDA parent skeleton of **5a** is found to be considerably strained. The bond angles at the sp^3 carbons, *i.e.*, C5–C6–C1

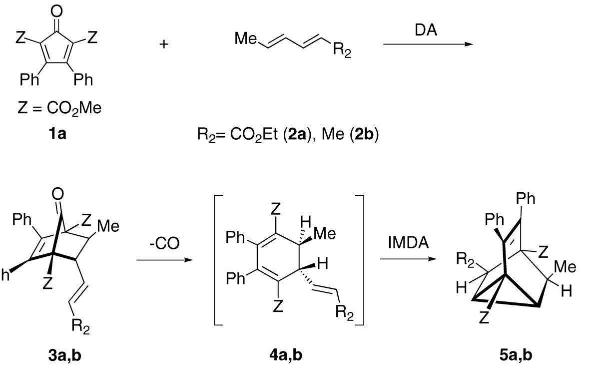

Chart 2

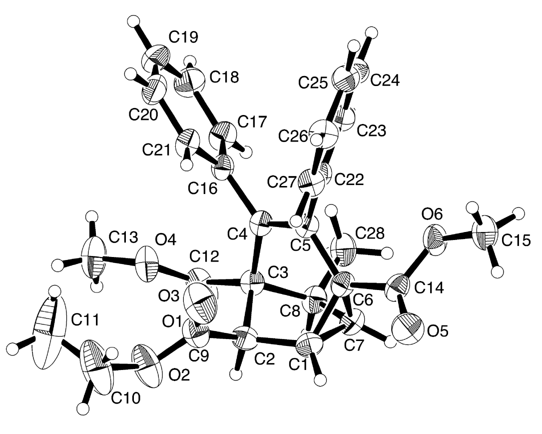

Fig. 1. ORTEP Drawing of **5a**

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(118.6°), C5–C6–C7 (117.8°), C6–C1–C2 (114.7°), and C6–C7–C8 (114.7°) deviate by 9.1°, 8.3°, 5.2°, and 5.2°, respectively, from the unstrained angle of 109.5°. The C2–C3 bond [1.582(3) Å] is found to be slightly elongated. The C1–C7, C1–C2, and C7–C8 bond lengths of 1.491(3) Å, 1.505(4) Å, and 1.506(4) Å, respectively, are significantly shorter than the typical single bond distance of 1.54 Å. To obtain additional structural details of the DDA adduct, DFT calculations were carried out on the basis of the formation pathway of **5a**. The important bond distances and angles of **5a** are summarized in Table 1, and the calculated structure is shown in Fig. 3. The DFT calculations at B3LYP/6-31G(d) level showed moderate bond elongation in the case of the C2–C3 bond (1.593 Å), indicating that there exist steric repulsions between the substituents (ester and phenyl groups). The calculated C1–C7 bond length of 1.494 Å is close to the experimental value. On the basis of highest occupied molecular orbital (HOMO) and lowest occupied molecular orbital (LUMO) interactions, Hoffmann predicted that the presence of electron-withdrawing substituents on cyclopropane can result in the lengthening of the vicinal bonds and shortening of the distal bond[14]; this is because the transfer of electron density from the HOMO of cyclopropane to the π^* orbital of the substituent decreases the antibonding electron density in the distal bond and the bonding electron density in the vicinal bonds. Other bond lengths and angles of the parent structure are satisfactory reproduced by the DFT geometry optimization.

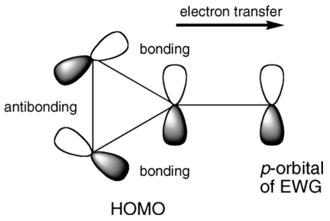


Fig. 2. Orbital Interaction of Cyclopropane HOMO and π^* Orbital of Substituent

Table 1. Comparison of X-Ray Structural Data of **5a** with Those Calculated by DFT

	Bond length (Å)			Bond angle (°)	
	X-ray	DFT		X-ray	DFT
C1–C2	1.505(4)	1.518	C2–C1–C6	114.7(2)	114.9
C1–C6	1.521(3)	1.529	C2–C1–C7	106.8(2)	106.9
C1–C7	1.491(3)	1.494	C6–C1–C7	61.9(2)	58.0
C2–C3	1.592(3)	1.593	C1–C2–C3	102.1(2)	101.6
C3–C4	1.526(3)	1.531	C2–C3–C4	108.7(2)	108.2
C3–C8	1.556(3)	1.571	C2–C3–C8	100.5(2)	100.6
C4–C5	1.349(3)	1.353	C4–C3–C8	108.8(2)	109.7
C5–C6	1.493(3)	1.500	C3–C4–C5	114.5(2)	114.7
C6–C7	1.549(3)	1.551	C4–C5–C6	117.0(2)	116.8
C7–C8	1.506(4)	1.515	C1–C6–C5	118.6(2)	118.4
			C1–C6–C7	58.1(1)	60.3
			C5–C6–C7	117.8(2)	118.5
			C1–C7–C6	60.0(2)	58.0
			C1–C7–C8	108.6(2)	109.2
			C6–C7–C8	114.7(2)	114.7
			C3–C8–C7	101.8(2)	101.4

In spite of the significant strain energy (27.5 kcal/mol[15]) observed in the structure of IMDA adducts containing the cyclopropane ring, these adducts were successfully obtained from the 5-vinyl-1,3-cyclohexadiene moiety. To elucidate the formation reaction behavior of **5a**, the DFT calculations at the B3LYP/6-31G(d) level were examined.

The heat of reaction of **5a** was calculated to be −1.6 kcal/mol, indicating that **5a** is more thermodynamically stable than **4a**. However, this heat of reaction is much smaller than that for the formation reaction of the less strained isotwistene system, *i.e.*, the IMDA reaction product of the decarbonylated DA adduct of **1a** and 1,5-hexadiene (−21.3 kcal/mol). This difference between the heats of reaction for the two compounds is attributable to the strain energy of the cyclopropane ring.

The stabilization of cyclopropane ring can be explained in terms of the effective frontier molecular orbital (FMO)[16,17] interaction between the HOMO of the cyclopropane ring and the LUMO of the electron-withdrawing group attached at the C6 position as described above.

Thus, the thermodynamic stability of the DDA adduct compensates for the instability introduced by the cyclopropane ring formation.

Contrary to our expectation, the estimated reaction barrier in the IMDA reaction was low (27.5 kcal/mol), and this value was comparable to that obtained in the case of the less strained isotwistene system (27.2 kcal/mol, $n=2$). In fact, heating of the DA adduct of 1,5-hexadiene ($n=2$) at 150 °C afforded the corresponding DDA adduct.[1] In addition, the calculated value is lower by 3.2 kcal/mol than the value obtained for the formation of the IMDA adduct ($n=3$) from the decarbonylated DA adduct of **1a** and 1,6-heptadiene. The smaller reaction barrier for the IMDA reaction may be attributed to the shorter tether system, whose movements are restricted.

The high IMDA reactivity is ascribed to the sterically favorable orbital interaction between the diene and the dienophile in the ground state (GS). The calculated confor-

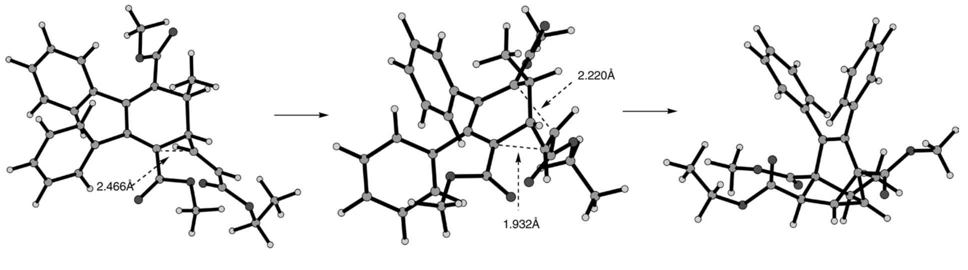
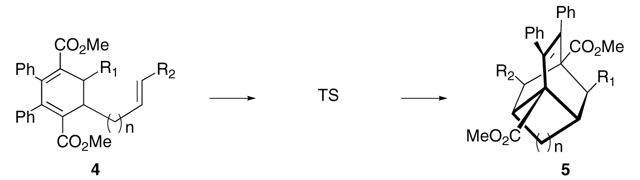


Fig. 3. B3LYP/6-31G(d) GS and Transition State (TS) Structures Formed in the IMDA Reaction of **4a**



n	R_1	R_2	E_{Triene} (**4**) (hartree)	E_{TS} (hartree)	E_{DDA} (**5**) (hartree)	reaction barrier (kcal/mol)	heat of reaction (kcal/mol)
0	Me	CO_2Et	-1534.64742 (**4a**)	-1534.60357	-1534.64995 (**5a**)	27.5	-1.6
2	H	H	-1306.80460	-1306.76130	-1306.83860	27.2	-21.3
3	H	H	-1346.09095	-1346.04200	-1346.12669	30.7	-22.6

Fig. 4. B3LYP/6-31G(d) GS and TS Energies for the IMDA Reaction of the Decarbonylated DA Adduct of **1a** and Unsaturated Dienes

mation of the precursor triene (**4a**) suggests that the GS geometry is very favorable for the IMDA reaction, wherein the interatomic distance between C1 of the diene and C6 of the dienophile is 2.466 Å; this bond length corresponds to the bond distance observed just before the saddle point is reached during the initial stages of DA reactions. The IMDA reaction of **4a** can be classified as 'neutral electron demand type' according to Sustmann's classfication[18] of cycloadditions in which the electron-withdrawing ester groups conjugated with the diene and the dienophile play an important role in determining the reactivity of the cycloaddition.

In summary, the DDA adducts containing a cyclopropane ring were formed by the thermal cascade reactions of **1a** with acyclic conjugated dienes. The DFT calculation results at the B3LYP/6-31G(d) level agreed well with the structural results of the DDA adduct by X-ray analysis; the DFT calculations also provided reliable mechanistic information on the formation of DDA adducts.

Experimental

Materials The DDA adduct (**5a**) was prepared by the previously reported method.[4]

Single Crystal X-Ray Analysis of 5a A single crystal of the DDA adduct **5a** was prepared by slow evaporation of its methanol solution at room temperature. A colorless prism crystal of **5a** with the approximate dimensions of 0.40×0.30×0.60 mm was mounted on a glass fiber. All measurements were performed on a Rigaku RAXIS RAPID imaging plate area detector with graphite-monochromated Mo$K\alpha$ radiation. The data were collected at a temperature of 23 ± 1 °C to a maximum 2θ value of 55°. The structure was solved by direct method (SIR-92[19]), and hydrogen atoms were placed at the calculation. The structure was refined by a full-matrix least-squares technique using anisotropic thermal parameters for non-hydrogen atoms and a riding model for hydrogen atoms. All calculations were performed using the crystallographic software package Crystal Structure.[20,21]

Crystal Data of **5a**: $C_{28}H_{28}O_6$, $M=460.53$, monoclinic, $a=16.695(1)$, $b=9.2674(6)$, $c=17.132(1)$ Å, $\beta=110.614(2)$°, $V=2480.9(3)$ Å^3, space group $P2_1/c$ (#14), $Z=4$, $D_c=1.233$ g/cm^3, Mo$K\alpha$ radiation, $\lambda=0.7107$ Å, $R_f=0.059$, $R_w=0.109$, GOF$=1.00$. The X-Ray crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (CCDC ref. No. 720526).

Molecular Orbital Calculation Semiempirical MO calculations were carried out on the CS Chem3D Pro interface using MOPAC93[7—9] on a Power Macintosh G4 or G5 computer. The calculated geometries and heats of formation were also examined by the improved PM5 method using the WinMOPAC (version 3.9) program.[10] The *ab initio* and density functional theory (DFT) computations were performed with Gaussian 03[12] on a HIT Linux cluster server composed of dual 1.6 GHz Itanium 2 processors. Geometry optimizations were performed using default convergence limits. Transition structures were located by using TS keyword. The nature of the stationary points were characterized by vibrational frequencies, which were used to obtain the thermodynamic parameters. Zero-point energy (ZPE) corrections were scaled by 0.9804.[22] The atomic coordinates of the optimized structures are available from our web site (URL http://pharm.ph.sojo-u.ac.jp/~kumayaku/).

Acknowledgements We thank Dr. T. Jikyo (Nakamura Gakuen University) for useful discussions and Mr. M.Nakatsu for experimental assistance.

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